# DISCUSSION

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During the last 40 years, laparoscopy has evolved from a limited gynecologic surgical procedure used only for diagnosis and tubal ligations to a major surgical tool used for a multitude of gynecologic and non gynecologic indications. Today, laparoscopy is one of the most common surgical procedures performed in many parts of the world.(116)

For many gynecologic procedures, such as removal of an ectopic pregnancy, treatment of endometriosis, or ovarian cystectomy, laparoscopy has become the treatment of choice. Compared with laparotomy, multiple studies have shown laparoscopy to be safer, to be less expensive, and to have a shorter recovery time. The advantages of the laparoscopic approach for other procedures, including hysterectomy, sacral culpopexy, and the staging and treatment of gynecologic cancers, continue to broaden.(117)

Gynecological laparoscopy is a commonly performed procedure. Providing anesthesia for this can present a challenge, particularly in the day surgery population. Poor analgesia, nausea, and vomiting can cause distress to the patient and increased cost for the health system, because of overnight admission.(117)

High-quality pain control after day-case surgery is still a major challenge. Although opioids continue to have an important role in postoperative pain management, they have side-effects. A multimodal approach has been suggested to improve postoperative analgesia and to reduce the opioid-related side-effects.(106)

In this study the effect of two different doses of pregabalin (75 mg and 150 mg) on post operative pain and analgesic consumption in patients undergoing laparoscopic gynecological surgeries was evaluated.

Pregabalin, is one of these drugs that is coming into focus. It is a structural derivative of the inhibitory neurotransmitter GABA although it does not bind to its receptors or to that of benzodiazepines. It was originally developed as spasmolytic agents. Its anticonvulsant, anxiolytic and sleep-modulating utility permitted its use as adjuncts for management of generalized or partial epileptic seizures resistant to conventional therapies. Its therapeutic armamentarium was furthermore expanded over time to control chronic pain conditions as began to gain popularity also in some acute painful conditions. It is well tolerated with good safety profile, and minimal adverse events the most commonly being dizziness and somnolence.(79)

The present study was carried out in Alexandria University Shatby Hospital on forty-five female patients belonging to ASA physical status I and II aged 30-60 years old scheduled for elective laparoscopic gynecological surgeries under general anaesthesia in a prospective, randomized, double blind study using closed envelope method and placebo controlled trial.

Patients were randomly categorized into three equal groups (fifteen patients each):

**Group I:** Patients received pregabalin 75 mg orally, hour before induction of anaesthesia with sips of water.

**Group II:** Patients received pregabalin150 mg orally, hour before induction of anaesthesia with sips of water.

**Group III:** Patients received a matching placebo orally, hour before induction of anaesthesia with sips of water.

Throughout the operative period, the hemodynamic profile was also checked when pregabalin was used, as it partially reflects its pain controlling ability and can index its intra-operative safety potentiality.

Result of the present study in comparison between three studied groups according to heart rate showed significant difference before induction (0.017), after induction, at 15 minute, at 30 minute, at 45 minute, at 60 minute, at 75 minute, after ETT extubation, at 6 hours, 12 hours, and at 18 hours (<0.001) as group III showed higher readings than the other two groups.

In comparison between the three studied groups according to mean arterial blood pressure there were statistically significant changes in these measurements after induction (0.038), at 15 minute, at 30 minute, at 45 minute, at 75 minute, at 90 minute, after ETT extubation at 6 hours, at 12 hours, at 18 hours, and at 24 hours (<0.001) as group III showed higher readings than other two groups.

In this respect, most of available literature[73,75] or clinical trial database,[118,119] did not declare any experimental or clinical haemodynamic alterations reported by the use of short or long term pregabalin. Accordingly, scare literature cared to comment on its simultaneous impact on intra-operative haemodynamic variables, when assessing its post-operative pain reducing potentialities, in the so many heterogeneous operative procedures that used pregabalin peri-operatively.[78,79,106]

Over some studies, few data did address the correlation between pre-operative pregabalin administration and the reduction in hemodynamic pressor response to airway instrumentation, during different operative surgeries;[120] of these, the one conducted by Gupta et al in relation to elective laparoscopic cholecystectomy.[121] All such studies did agree on the benefits of the drug, to significantly decrease the significant increase in heart rate and blood pressure provoked by the noxious painful and stressing stimuli of laryngoscopy and intubation.[122-124] Though with different perspectives, those studies are considered in agreement with the current findings, reporting the significant reduction in those two parameters especially after intubation. More-over the attenuation was pertained stabilized with minimal haemodynamic fluctuations, in their studies and in the current work, where blood pressure remained significantly reduced throughout the intra-operative period.[120,121]

The explanations set by Rastogi et al and Gupta et al for pregabalin utility in ameliorating such pressor responses were based on their simultaneous findings of pre-operative dose-related sedation induced by the drug in their study series.[120,121] But since no significant sedation was relevantly found in the current work, one is in favor to adopt reasoning the haemodynamic stability encountered, to the anxiolytic potentialities of pregabalin, raised in previous literature as that of Lauria-Horner and Pohl[95] and Baldwin et al.[119] This aside its pain ameliorating properties currently observed and previously established using the same tested pregabalin dose in different clinical trials as that of Agarwal et al,[116] Cabrera Schulmeyer et al,[117] and Freedman and O'Hara.[125]

During the early post-operative period the primary end point of the present work was targeted to assess the effect of pre-operative pregabalin on pain intensity as scored by VAS. In this respect, comparison between three studied groups during rest (static) showed significant changes in these readings arrival to ward (<0.001), after 30 minutes(<0.001), after 60 minutes(<0.001), after 90 minutes(<0.001), after 120 minutes(<0.001), after 3 hours(0.002), after 4 hours(<0.001), after 6 hours(0.009), after 14 hours(0.014), and after 20 hours(<0.001) as group III showed higher readings than other two groups.

In comparison between three studied groups during cough (dynamic) showed statistically significantly differences in these readings arrival to ward (<0.001), after 30 minutes (<0.001), after 60 minutes (<0.001), after 90 minutes (<0.001), after 120 minutes (0.002), after 3 hours (<0.001), after 4 hours (0.002), after 6 hours (0.008), after 14 hours (0.018), and after 20 hours (0.001) as group III showed higher readings than other two groups.

Such reduction in pain intensity by the current preemptive use of pregabalin, was also reported in some previous studies, conducted in settings of laparoscopic cholecystectomy as that of Agarwal et al,[116] other day case procedures as that of Kim et al,[126] or even major surgeries as that of Reubin et al.[127] This, despite the fact, that such studies did not necessarily share in common, the same pregabalin dosing, nor the same time scheduled and methods adopted for pain intensity scoring.

Focusing on laparoscopic gynecological surgeries, Jokela et al[128] where the drug was used in women undergoing day-case gynaecological laparoscopic surgeries at doses of 75 and 150mg in conjunction to ibuprofen. Also it was in line with that reported by Cabrera Schulmeyer et al.[117]

On comparing the other laparoscopic, daycare or minor surgery that used pregabalin, the current findings were in agreement to the comparable study of Agarwal et al[116] that used the same pre-operative dose of pregabalin versus placebo, reported a significant reduction in post-operative pain intensity, as assessed by VAS at zero time and at 4 hours interval till the end of 24$^{th}$ hour. The only difference was that their median VAS scores were set higher, both at rest or during cough, whether by placebo or induced by pregabalin. This could be appraised as ethnicity difference among patients,[129,130] because the dermographic data appeared rather similar in the two studies.

In a second study conducted by Peng et al,[131] testing low dose pregabalin (50 and 75mg), the significant reduction in postoperative pain intensity as assessed by verbal rating score (VRS), only lasted for 45 minutes by the smaller dose and up to 90 minutes by the bigger. Such similarity in timing, for maintaining pain reduction by 75mg in theirs and 150mg in our study, favor the notion which states that pregabalin, is at its best of pain control, during the immediate postoperative period. However, there was a limitation in comparing reduction in pain intensity between the two studies from 12$^{th}$ hour thereafter, because they then, re-administered their tested doses again, to cover the remaining 24 hours post-operative period.

Also it was in line with that reported by Cabrera Schulmeyer et al,[117] in patients undergoing laparoscopic sleeve gastrectomy at a dose of 150mg.

Moreover, the pain reduction was equivocal or some times better attenuated by the use of a bigger pregabalin dose of 300mg, as in those undergoing third molar extractions by Hill et al[132] or elective abdominal hysterectomy by Ittichaikulthol et al,[133] but at the expense of developing adverse effects.

It is clear that the optimal dosing of pregabalin for attenuating early postoperative pain management is still debatable in most literature, bouncing in ranges from 50 to 300 mg, if safety is also to be considered.[125,131,134-136] Such variation in dosage was partially attributed to the type of operation in question and the nature of presenting pain to control.[137,138]

Yet what was agreed upon by most authors is the explanation as to why pregabalin is now gaining greater popularity in controlling acute postoperative pain.[139,140] This resides on the drug's ability to reduce hyperexcitability of dorsal horn neurones induced by tissue

damage rather than to suppress the afferent input from the site of tissue injury[79,107-110] This is achieved by binding of the drug to the α2-δ subunit of presynaptic, voltage-dependent calcium channels that are widely distributed there.[8,141] This will stabilize their cellular trafficking, to allow for the transient inhibition of Ca influx, thereby reducing release of several excitatory neurotransmitters (glutamate, norepinephrine, serotonin, dopamine, SP and CGRP) involved in such sensitization.[86,88,91,92,142]

In difference to the current findings, some studies deny the efficacy of preemptive pregabalin in attenuating acute postoperative pain and even claim that there is no evidence to support its benefit in acute pain reduction.[78,106]

For example, Paech, et al, in a randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery found that a single preoperative dose of 100 mg pregabalin does not reduce acute pain or improve recovery after minor surgery involving only the uterus.

Also, In the work of Chang et al[143] in link to laparoscopic cholecystectomy, the administration of 300mg pregabalin in two perioperative doses 12 hours apart, starting at an hour preoperative, failed to significantly attenuate the intensity of post laparoscopic shoulder pain as scored by VRS. This existing discrepancy between their findings and the current work, resides on the existence of many divergent variables; i.e. methodology of pain intensity scoring and most importantly the quality of pain assessed.[106,137,138] Thus, in most of the trials, abdominal pain (with its visceral > parietal components) was the main target to attenuate, being induced by traumatic and inflammatory tissue injury which evoke hyperalgesia due to central sensitization.[139,141,144] While postoperative shoulder pain, is different. It is triggered by local acidosis, or distension of the diaphragm, which leads to acute irritation more than injury of the phrenic nerve.[145-151] Because of such difference, it would be expected that the anti-nociceptive action of pregabalin, in settings of neural sensitization after tissue injury, is likely to attenuate abdominal pain, rather than reacting against phrenic irritation inducing shoulder pain.[152-157]

When other heterogeneous groups of surgeries, performed under general or spinal anesthesia were taken in consideration in pooled data from 14 randomized clinical trials in the work of Baidya et al,[79] the results failed to confirm pregabalin efficacy to significantly attenuate early post-operative pain, in 7 of them. Just previous to that, the meta-analysis conducted by Zhang et al,[106] pooled from 11 valid randomized, controlled clinical trials with 16 treatment arms were also insignificant regarding pregabalin's acute pain reducing potentials. Though on individual bases, their analysis admitted, that pregabalin succeeded to attenuate such acute postoperative pain significantly, in some of such studies, when compared to placebo.

Interestingly, most studies enrolled in that same meta-analysis of Zhang et al,[106] reported a simultaneous significant reduction in opioid consumption in the first 24 hours postoperatively when pregabalin was used.[117,133] This highlights the importance of calculating the amount of analgesic consumed, when monitoring changes in pain intensity.

In the present study, analgesic consumption was taken as a surrogate indicator, when assessing the efficacy of pregabalin in reducing immediate postoperative pain following laparoscopic gynecological surgeries.

Current results cleared that the total dose of analgesia (ketrolac) consumed during the studied time postoperatively, In comparison between three studied groups according to the time of first dose of analgesia showed significant change (<0.001) as group III needed earlier analgesia than two other groups.

Such result is in agreement with the opioid-sparing potentialities of pregabalin, generally observed in most of the studies enrolled in the different aforementioned meta-analysis.[79,106,158,159] This despite the fact, that in some individual studies, a simultaneous reduction in pain intensity was not found.[134,135] Vice versa the opioid-sparing potentials of the drug was not in parallel assessed.[128,160] The third option, was that the reduction of cumulative opioid consumption by pregabalin was being totally denied.[141,160,161]

For instance, when contrasting the three studies assessing immediate postoperative pain following laparoscopic cholecystectomy, it was clear that only one of them was in agreement with the current findings. This reported a significant reduction in the patient-controlled fentanyl consumption in the first 24 hours postoperatively following a single pre-operative dose of 150mg pregabalin.[116] While that of Peng et al differed, where there was no significant fentanyl-sparing benefit reported, by the use of pre-operative low doses of pregabalin (50 or 75mg being repeated after 12 hours post-operatively).[131] In the third study conducted by Cheng et al, 300mg pregabalin did not significantly alter the cumulative ketorolac consumption in settings of post-operative shoulder pain following laparoscopic cholecystectomy, when compared to placebo.[143] It was obvious, that the dose of pregabalin used, versus the nature of pain assessed, in face of the opioid selected, by the different regimens adopted, are all variables dictating the outcome of pregabalin's opioid-sparing benefits.[131,139,159]

Some of these variables did also matter and seemed to contribute when interpreting the contradictory results between those with or against the present findings, that were obtained from pooled data of heterogeneous surgical procedures, but were all probing in the utility of pregabalin perioperatively.[78,79,106,159] It is worth noting, that for sake of comparison between them, the cumulative-narcotic intake was calculated as weighted mean difference (WMD), whenever narcotics were given for more than 24 hours.[106]

When looking among them, five studies versus four in the meta-analysis of Zhang et al and eight studies versus three in that of Baidya et al were in agreement to the current findings regarding the significant reduction in opioid consumption by pregabalin.[79,106] Moreover, the relevant doses of pregabalin used were correlated to the extent of reduction in amount of cumulative opioid-consumed in Zhang et al analysis.[106] Thus, their combined data showed significant opioid sparing effect of -8.80 mg WMD in the studies that used a single dose preoperative pregabalin <300mg day. Some of these were of patients undergoing, day-case gynaecological laparoscopic surgery or laparoscopic sleeve gastrectomy in their series[117,135] or augmentation mammoplasty and cardiac surgeries[126,137] in Baidya et al series. While in those using pregabalin >300 mg, whether administered as a single preoperative dose or as two separate doses (1hour before operation and 12 hours after the first dose), their combined data showed significant reduction in opioid consumption amounting to −13.40 mg WMD. Some of these were of patients undergoing hip arthroplasty or abdominal hysterectomy in their series[133,134] or robot-assisted endoscopic thyroidectomy and spinal fusion[126,127] in Baidya et al series.

On the contrary, the studies that disagree with the opioid-sparing ability of pregabalin shown in this study, explain that the benefits of the drug in this respect only becomes significantly apparent, in those patients initially suffering preoperatively from chronic pain, or are having procedures conducted at site of pain or are having otherwise extensively painful surgical procedures.[161] That is why their post-operative 12-hour oxycodone consumption in laparoscopic hysterectomy by Jokela et al[128] or 24-hours morphine consumption in abdominal hysterectomy by Mathiesen et al[162] were not found reduced as explained in their studies when pregabalin was given pre-operatively.

At this juncture, few authors did extended in their studies, the estimation of time to initial rescue analgesic as an additive index whenever assessing the pain reducing potentials of any drug. That is why, in the current study, we cared to report the time needed for initiation of first dose of analgesia during the 24 hours post-operative period.

In group I the time of first dose of analgesia ranged from 1.50 hours to 8.0 hours with mean of 5.90±2.25, In group II the time of first dose of analgesia ranged from 1.50 hours to 14.0 hours with mean of 7.37±3.22, and In group III the time of first dose of analgesia ranged from 0.0 hours to 2.0 hours with mean of 0.33±0.7.

Such finding is in partial agreement to the study of Saraswat and Arora showing the time to first analgesia (was *a NSAIDs*), being 14.17 hours by the use of 300mg pregabalin pre-operatively when given in heterogenous surgeries done under spinal anesthesia.[163] However, the delay in their initiation timing to first-dose analgesic more than that reported in ours could be attributed to them using double pregabalin doses, in settings of spinal anesthesia.

Yet, current finding differed from reports of Jokela et al declaring that the time to first rescue dose analgesic was found none significantly altered by pregabalin (75 or 150 mg) given pre-operatively with ibuprofen in day-case gynaecological laparoscopic surgeries.[135] Neither was it altered, by 300mg pregabalin, in the study of Cheng et al looking at postoperative shoulder pain, after laparoscopic cholecystectomy.[143] It is obvious, that the discrepancy between their findings and current observation, could not be totally explained in light of the difference in the used pregabalin dosage but is rather due to the variability in regimens and procedures adopted in the varied literatures, that makes comparison between them, sometimes unequivocal. Moreover, the scarce number of trials that measured 'time to first analgesics' are small and thereby could not be statistically enrolled in the different meta-analysis as stated by Zhang et al.[106] This obliges one to consider findings around this point, still not conclusive, and needs to be explored in larger trials.

When taken collectively, the benefits of pregabalin in pain reduction by the different estimates adopted (pain attenuation + narcotic-sparing + time to first analgesics) in this current study can collectively be interpreted in light of conclusions drawn by some publications. These state, that benefits of pregabalin in pain control were only shown in studies designed to use it, as preemptive analgesic in laparoscopic, daycare, and minor surgeries, which are not very painful.[79,106] Indeed, the current study applies to these types of surgeries mentioned, when 75,150mg pregabalin was tested for control of immediate postoperative pain following laparoscospic gynecological surgeries.

Once justifying efficacy and benefits, the current study cared to check on some of the postoperative side effects that were claimed to develop in some previous reports when using different doses of pregabalin for peri-operative pain management.[128,132,134]

When focusing on post-operative sedation, current findings did not witness any significant difference in Ramsay sedation score, when patients receiving single dose of75mg or 150mg pregabalin were compared to controls. This is in agreement to findings of R. Jokela et al who used, the same pregabalin dose and sedation assessment score, in context of testing pregabalin ability to reducing post-operative pain in gynecological laparoscopic surgeries.[135] These same patterns, of being with[133,135] absence of sedation was also reported by the heterogeneous surgery studies, of Agraweel et al who used, the same pregabalin dose and sedation assessment score, in context of testing pregabalin ability to reducing post-operative pain in laparoscopic cholecystectomy.[116] The same applies to data reported by Peng et al when they assessed such side effect while using smaller pregabalin doses (50 and 75mg).[131]

The third study in the laparoscopic cholecystectomy series of Cheng et al did differ, whereby they recorded a significant over-sedation in the first two hours post-operatively by 300mg pregabalin when compared to placebo.[142]

These same patterns, of being with[133,135] or against[126,161] evaluating the post-operative pain controlling ability of pregabalin (where sedation was their secondary end-point), in the different meta-analysis aforementioned.[78,106,128] In all, pregabalin induced side effects, including sedation, appeared to be dose dependent, i.e becoming significant when ≥ 300mg of the drug is being used.[79,106,166] This was ascertained by findings of White et al in their dose-ranging study on pregabalin that addressed sedation itself as their primary end-point.[138]

When PONV, which is triggered as a resultant of surgical manipulations and opioid side effects[128,137,138,165] was currently addressed in this work, one had hoped that pregabalin could significantly minimize such adverse action, especially that the drug showed a concomitant opioid-sparing effect and is being used in doses much less than 300mg. Yet, this was not the case where the apparent reduction in this parameter was statistically found insignificant; there were no any significant changes between three studied groups.

Despite of this, current findings are still in agreement with the insignificant changes, in PONV reported by the three studies that assessed different doses of pregabalin on acute post-operative pain in laparoscopic surgries. Of these, only that of Agraweel et al, was sharing our current finding of inducing a simultaneous opioid-sparing benefit that did not correlate with the promise of finding a significant reduction in PONV.[116] The data from the other two cholycestectomy studies did not record an opiate-sparing utility making their insignificant reduction in PONV more acceptable.[131,143] It seems that the operative maneuvers, ethnicity, social and psychological difference among the individual patients recruited in the different studies, can play a role in modulating such parameter.[166,167]

Also, the insignificant changes in other associated side effects, induced by pregabalin, in the present study, seem to follow the general theme observed in the respective comparative laparoscopic surgries studies assessing pregabalin on acute post-operative pain.[125,126,128,164] This despite each study in its own commented on a set of overlapping side effects that were all claimed to be evoked whether by operative or non-operative use pregabalin.[73,138,158] Theirs and our results differ from collective pooled data in meta-analysis of Zhang et al which concluded that the drug managed to significantly reduce opioid-related adverse side effects after surgery in the context of reducing opioid consumption.[106] A third different conclusion was drawn by Engelman and Cateloy stating that pregabalin, provides additional analgesia, but at the cost of additional adverse effects, when they contrasted pooled results from 18 heterogeneous surgeries using the drug peri-operatively.[159]

From the primary end points assessed in this work, one can declare, that usage of a dose 150 mg of prgabaline was more effective in reducing hemodynamic changes, post operative pain intensity, and analgesic consumption in comparison of a dose 75 mg of prgabaline as preemptive analgesia, when neither doses caused respiratory depression or sedation or any post operative side effects as a secondary end point assessed.

# SUMMARY

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Since the introduction of laparoscopic as alternative to traditional laparotomy, postoperative pain has been generally reduced. However, it can still peak, especially during the early postoperative period and becomes the main cause of overnight hospital stay and prolonged convalescence after this day-case surgical procedure.

Though opiates were used for long, to ameliorate such immediate postoperative pains, yet still this was at the expense of concurrently inducing sedation, nausea and vomiting, adding more to the possibility of in-hospital stay. Thus, optimizing postoperative pain relief, not only to sub-serve reduction of its intensity but to also enhance the recovery and shorten length of stay became the broader target of multimodal pain control regimens nowadays. That is why; searching for a drug that would be effective in reducing pain, safe from major adverse effects and can meanwhile possess an opioid-sparing potentiality would be a merit so as to improve the success rate of ambulatory day-care surgeries as that of laparoscopic gynecological surgeries.

Pregabalin, is one of these drugs that is coming into focus. It is a structural derivative of the inhibitory neurotransmitter GABA although it does not bind to its receptors or to that of benzodiazepines. It was originally developed as spasmolytic agents. Its anticonvulsant, anxiolytic and sleep-modulating utility permitted its use as adjuncts for management of generalized or partial epileptic seizures resistant to conventional therapies. Its therapeutic armamentarium was furthermore expanded over time to control chronic pain conditions as began to gain popularity also in some acute painful conditions. It is well tolerated with good safety profile, and minimal adverse events the most commonly being dizziness and somnolence.

Thus the present study was carried out to evaluate the effect of two different doses of pregabalin on post operative pain and analgesic consumption in patients undergoing laparoscopic gynecological surgeries.

After approval of Ethical Committee of Faculty of Medicine and having written informed consent from patients, the present study was carried out in Alexandria University Shatby Hospital on forty-five female patients belonging to ASA physical status I and II aged 30-60 years oldscheduled for elective laparoscopic gynecological surgeries under general anaesthesia in a prospective, randomized, double blind study using closed envelope method and placebo controlled trial.

Patients were randomly categorized into three equal groups (fifteen patients each) patients received pregabalin 75 mg, 150 mg and placebo orally, hour before induction of anaesthesia with sips of water.

After a written informed consent from each patient, all the patients were assessed pre-operatively by detailed history taking, complete clinical examination, airway assessment, and routine laboratory investigations. Each patient received pregabalin 75 mg or 150mg or a matching placebo and were administered orally, in the ward 1 h before induction of anaesthesia with sips of water. On arrival to the operating room, patients were connected to the standard monitoring; including electrocardiograph, non-invasive arterial blood pressure, and pulse oximeter. They were all subjected to the same anaesthetic protocol. Induction was commenced by the administration of IV fentanyl 3 μg/kg followed after 5 min by injection of IV xylocaine 1 mg/kg then was followed after 1 min by IV propofol 2 mg/kg, followed by IV injection of cisatracurium 0.2mg/kg to facilitate

endotracheal intubation. Anaesthesia was maintained with isoflurane 1%-1.5% in 100% oxygen along with a maintenance dose of cisatracurium 0.02 mg/kg every 30 min until the end of the operation. After fulfilling criteria of extubation patients will be extubated and will be fast-tracked to the ward to according to the modified Aldrete score,[10] when their score will be ≥ 9.

In the ward, patients will receive intravenous of ketrolac with dose not exceed 30 mg/ 6hwhen the VAS scores more than or equal 4.

# The following parameters were assessed in the present study

## A. Hemodynamic Parameters

Heart rate (beats/minutes), Mean arterial blood pressure and Arterial oxygen saturation ($SpO_2$)

These will be monitored continuously and recorded at the following times:

Before induction, after induction, Every 15 minutes intraoperative, After endotracheal extubation and Postoperative every 6 hours for 24 hour

## B. Postoperative pain

1. Assessment of pain both at rest (static) and during coughing (dynamic). It will be assessed using visual analogue scale (VAS).

### *Assessment of pain will be done*

1. On arrival of patient to the ward.
2. Then every 30 minutes in the first two hours.
3. Then every one hour till six hours
4. Then every 6 hours for the rest of 24 hours.
5. When postoperative pain is VAS 4, patients will receive intravenous ketrolac with dose not exceed 30 mg/ 6hour and the total administered dose in 24 hour and requirement time will be recorded.

## C. Analgesic consumption

It will be assessed as follows:

3. First dose required.
4. Total requirement in 24 hours.

## D. Level of sedation

It will be assessed with the Ramsay sedation score

Patients with a sedation scale of 4 will be considered as sedated. Assessment of sedation will be done on arrival of patient to the ward and then every 6 h till the end of the study, that is, 24 h after operation.

## E. Postoperative nausea and vomiting

The severity of PONV was assessed first 24 hours.

## F. Postoperative side effects

Patients will be observed for any side effects during the first 24 hours.

Result of this study showed Regarding hemodynamic changes the comparison between three studied groups according to heart rate showed significant difference before induction, after induction, at 15 minute, at 30 minute, at 45 minute, at 60 minute, at 75 minute, after ETT extubation, at 6 hours, 12 hours, and at 18 hours as group III showed higher readings than the other two groups. These findings agreed with reading of mean arterial blood pressure in the three studied groups; In comparison between the three studied groups according to mean arterial blood pressure there were statistically significant changes in these measurements after induction, at 15 minute, at 30 minute, at 45 minute, at 75 minute, at 90 minute, after ETT extubation at 6 hours, at 12 hours, at 18 hours, and at 24 hours as group III showed higher readings than other two groups.

On assessment of pain at rest (static) according to visual analogue scale (VAS) Comparison between three studied groups There was a significant change in these readings arrival to ward, after 30 minutes, after 60 minutes, after 90 minutes, after 120 minutes, after 3 hours, after 4 hours, after 6 hours, after 14 hours, and after 20 hours($<0.001$) as group III showed higher readings than other two groups.

On assessment of pain at cough (dynamic) according to visual analogue scale (VAS) Comparison between three studied groups There were statistically significantly differences in these readings arrival to ward, after 30 minutes, after 60 minutes, after 90 minutes, after 120 minutes, after 3 hours, after 4 hours, after 6 hours, after 14 hours, and after 20 hours as group III showed higher readings than other two groups.

In comparison between three studied groups according to the time of first dose of analgesia showed significant change as group III needed earlier analgesia than two other groups.

In comparison between the three studied groups according to total analgesic consumption showed significant change as group III needed more analgesia than two other groups.

Comparison between three studied groups according to level of sedation assessed by Ramsay sedation score there was a significant change only on arrival to ward as patients were more sedated in group I and group II than group III showed.

There were no any significant changes between the three studied groups according post operative nausea and vomiting.

There were no any significant changes between the three studied groups according post operative side effects.

**<u>As a conclusion to this study</u>**

From the primary end points assessed in this work, one can declare, that usage of a dose 150 mg of prgabaline was more effective in reducing hemodynamic changes, post operative pain intensity, and analgesic consumption in comparison to a dose 75 mg of prgabaline as preemptive analgesia, when neither doses caused respiratory depression or sedation or any post operative side effects as a secondary end point assessed.

**Thus in light of previous conclusion, one could recommend:**

1- The need for more clinical studies to identify the appropriate dose that can also induce a significantly simultaneous reduction in PONV while pertaining the same pain reducing utility and the same safety profile in the same operative settings.

2- The need for more clinical studies to justify the best appropriate dose and timing for pregabalin use in control of intubation stress response that would stabilize the haemodynamic variables and secure respiration both intra- and post-operative.

3- The need for further studies to expand the use of the drug in control of post-operative pain and to decrease the use of opiates in other surgeries that are more painful or may need more analgesic consumption.

# CONCLUSIONS

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1. Usage of a dose 150 mg of prgabaline was more effective in reducing hemodynamic changes in comparison of a dose 75 mg of prgabaline as preemptive analgesia in laparoscopic gynecological surgeries.
2. Usage of a dose 150 mg of prgabaline was more effective in reducing pain intenisty in comparison of a dose 75 mg of prgabaline as preemptive analgesia in laparoscopic gynecological surgeries.
3. Usage of a dose 150 mg of prgabaline was more effective in reducing postoperative analgesic consumption in the first 24 hours postoperatively in comparison of a dose 75 mg of prgabaline as preemptive analgesia in laparoscopic gynecological surgeries.
4. Usage of a dose 150 mg of prgabaline could delay the time needed for intiation of any analgesics more in comparison of a dose 75 mg of prgabaline as preemptive analgesia in laparoscopic gynecological surgeries.
5. Neither doses caused respiratory depression or did alter the sedation score postoperatively.
6. Neither doses caused suppress PONV.
7. Neither doses caused post operative side effect

# RECOMMENDATIONS

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1. The need for more clinical studies to identify the appropriate dose that can also induce a significantly simultaneous reduction in PONV while pertaining the same pain reducing utility and the same safety profile in the same operative settings.
2. The need for more clinical studies to justify the best appropriate dose and timing for pregabalin use in control of intubation stress response that would stabilize the haemodynamic variables and secure repiration both intra- and post-operative.
3. The need for further studies to expand the use of the drug in control of post-operative pain and to decrease the use of opiates in other surgeries that are more painful or may need more analgesic consumption.